72 year-old with poorly controlled blood pressure

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Endorama May, 29 2014

HPI:

- The pt presented to OSH with c/o weakness and frequent falls for one week.
- He was initially alert and following commands but subsequently became hypotensive with SBP to the 80s. He received IVF with improvement in hypotension but continued to have labile BP ranging from SBP 80-200.
- While in the ER he became nonverbal and unresponsive with a possible seizure and was intubated for airway protection and admitted to the ICU.
- 5 days later the pt was transferred to UofC for further management.

PMH:

- HTN
- DM2
- Hypercholesterolemia
- Aortic valve replacement

FH and SH:

- FH was not available, the pt had no family and his friend was a decision maker for him
- SH (limited): no alcohol abuse, no smoking, no illegal drug use

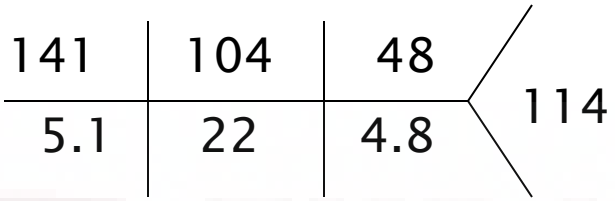
Meds prior to admission:

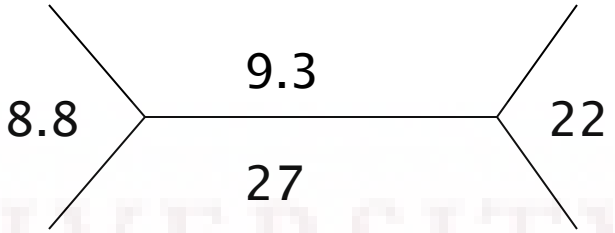
- Norvasc 10mg/day
- Metoprolol 100mg BID
- Losartan 50mg/day
- Glipizide 5mg/day
- Pravastatin 40mg/day
- Omeprazole 20mg/day
- Warfarin

Physical examination:

- Vitals: **BP 202/80, Pulse 103,** Resp 22, Wt 114.8 kg, SpO2 99%.
- Constitutional: Patient appears well-developed, well-nourished, **sedated and intubated.**
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: Mucous membranes moist.
- Neck: Palpable thyroid, **L sided nodule 2cm in size.**
- Cardiovascular: Regular rate. Intact distal pulses.
- Respiratory/Chest: on vent. No wheezing, **bilateral crackles.**
- Gastrointestinal/Abdomen: NG suction in place.
- Musculoskeletal/extremities: **edema UE. Fungal infection of toe nails.**
- Neurological: **AAOx0. Sedated and intubated.**
- Skin: Skin is warm and dry. **Acanthosis nigricans of neck.**

Labs:





Ca 7.2 (8.4-10.2 mg/dL),
Phos 7.8 (2.5-4.4 mg/dL)
Mg 2.5 (1.6-2.5 mg/dL)

LFTs:
Total Protein 5.3 (6-8.3 g/dL)
Albumin 3.5 (3.5-6 g/dL)
Total Bilirubin 2.5 (0.1-1 mg/dL)
Bilirubin, conjugated 1.5 (0-0.3 mg/dL)
Alk Phos 58 (30-120 U/L)
AST 1836 (8-37 U/L)
ALT 573 (8-35 U/L)

HA1C 6.4%

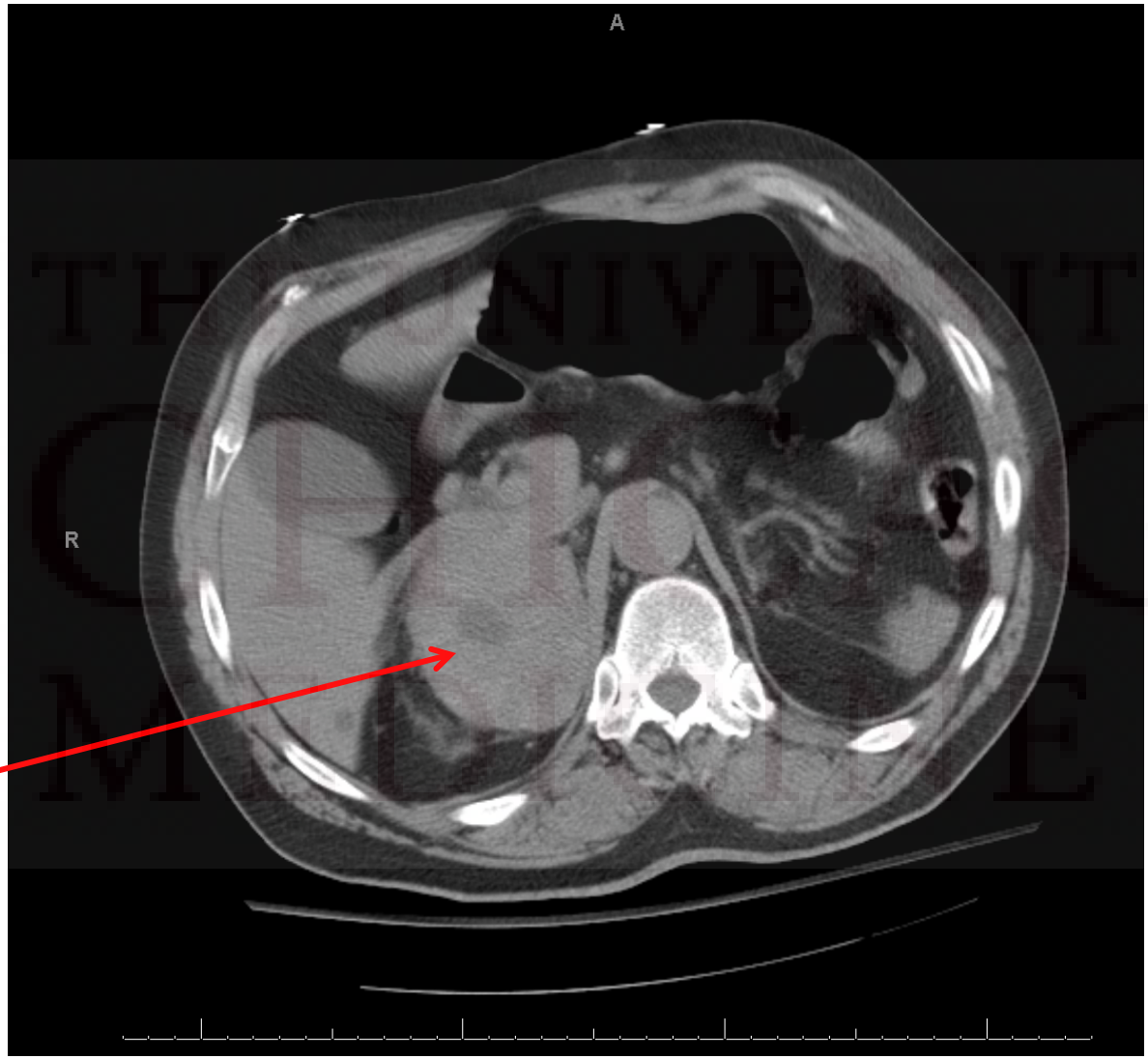
TSH 0.18 (0.3-4 mcU/mL)
FT4 0.79 (0.9-1.7 ng/dL)
TT3 38 (80-195 ng/dL)
Reverse T3 1342 (160-353 pg/mL)

LDH 6051 (116-246 U/dL)
CK 178180 (9-185 U/L)

Labs:

- random cortisol 42.2 mcg/dL
- ACTH 51.4 pg/mL
- normetanephrine 19.6 (0–0.89) nmol/L
- metanephrine >50 (0–0.49) nmol/L
- renin 17 ng/L
- aldosterone 26 ng/dL

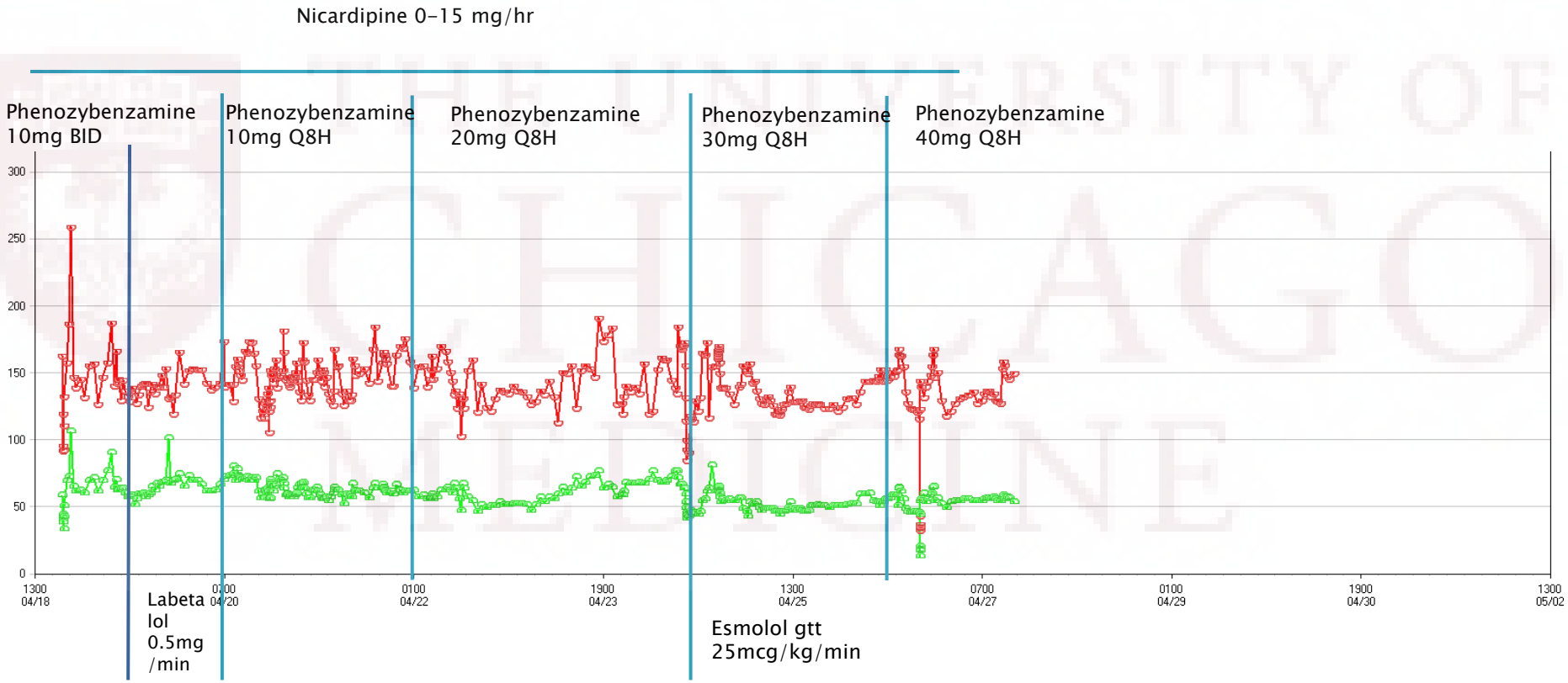
CT:



Management:

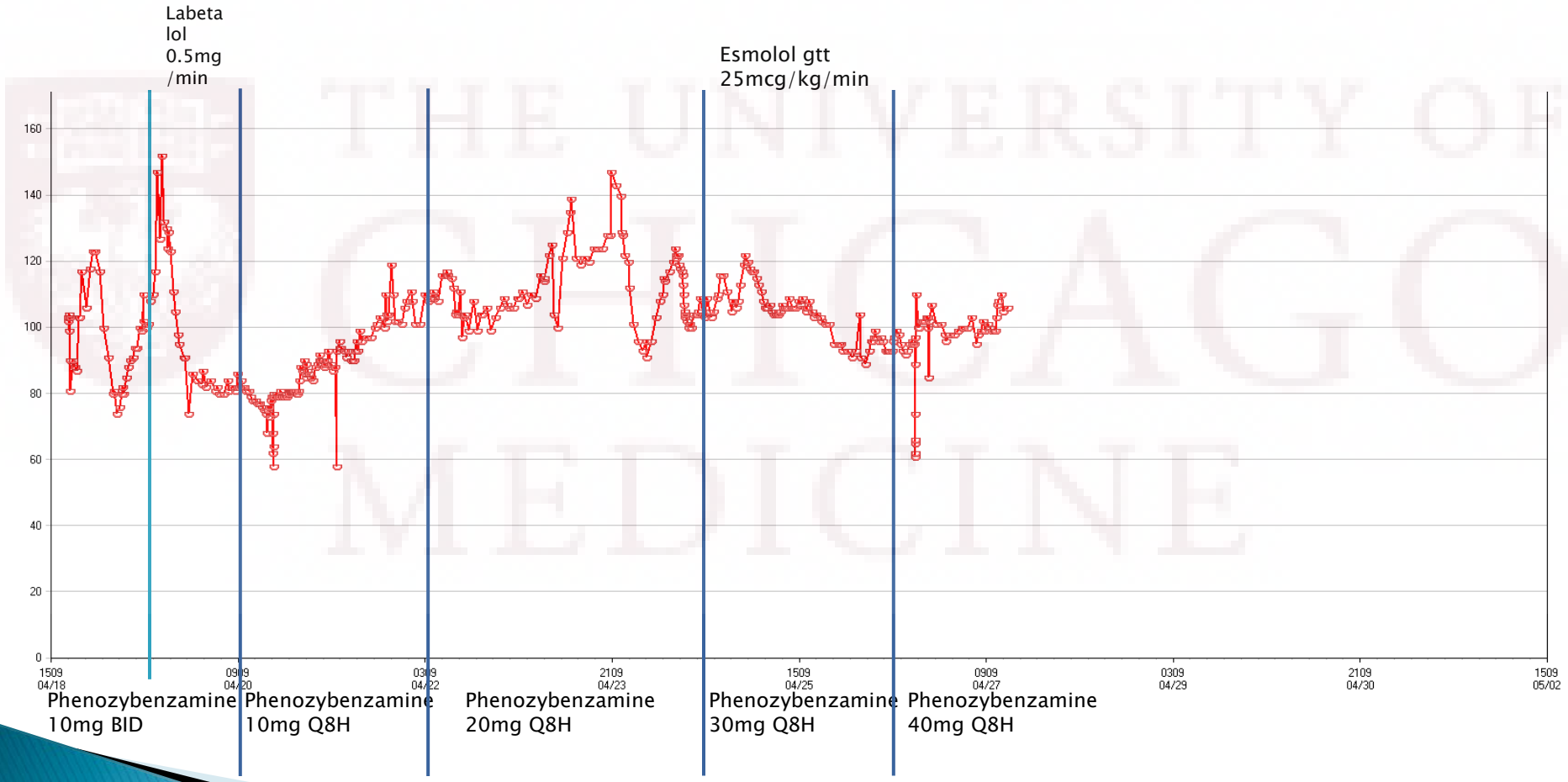
- 04/13 The pt was also started on phenoxybenzamine 10mg BID
- 04/16 the pt was changed to prazosin 1mg Q8H
- 04/17 the pt was changed to 0.5mg Q8H
- 04/18 the pt was transferred to UofC, prazosin was discontinued and the pt was started on phenozybenzamine 10mg BID

SBP and DBP:


Nicardipine 0-15 mg/hr
Phenozybenzamine 10mg BID
Phenozybenzamine 10mg Q8H
Phenozybenzamine 20mg Q8H
Phenozybenzamine 30mg Q8H
Phenozybenzamine 40mg Q8H
300
250
200
150
100
50
0
1300 04/18
0700 04/20
0100 04/22
1900 04/23
1300 04/25
0700 04/27
0100 04/29
1900 04/30
1300 05/02
Labetalol 0.5mg/min
Esmolol gtt 25mcg/kg/min

HR:

Nicardipine 0-15 mg/hr



- Due to multi-organ system failure, high risk for surgery and poor prognosis, the pt was made DNR/DNI and comfort care on 04/27/14
- The pt was extubated and died at 2PM on 04/27/14

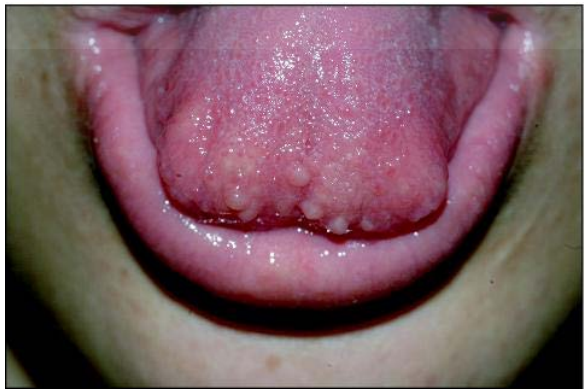
- Pheochromocytoma and genetic syndromes
- Who should be screened?
- Preoperative management of pheochromocytoma
- Pheochromocytoma and rhabdomyolysis

- Pheochromocytoma is a rare tumor originating from adrenal medulla, usually characterized by secretion of catecholamines and associated signs and symptoms of catecholamine excess.

- Several syndromes are associated with pheocrhomocytomas

- **MEN type 2:**
  - autosomal dominant pattern
  - 2a (Sipple syndrome): medullary thyroid carcinoma, pheochromocytoma, hyperparathyroidism.
  - 2b: mucosal neuromas, pheochromocytoma, medullary thyroid cancer.

Both have mutations in RET gene (2a – mutations affecting extracellular RET domain, 2b – mutations affecting intracellular RET domain).



- **VHL:**
- Autosomal dominant pattern, several types:
- Type 2 VHL: 2a – pheochromocytoma, hemangioblastoma, low risk of renal cell carcinoma;

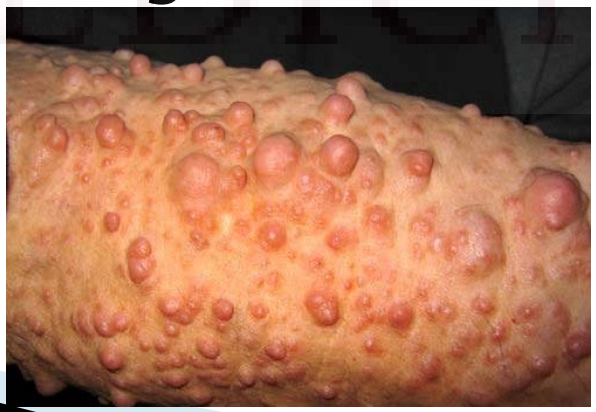
2b – pheocrhomocytoma, hemangioblastoma, high risk or renal cell carcinoma;

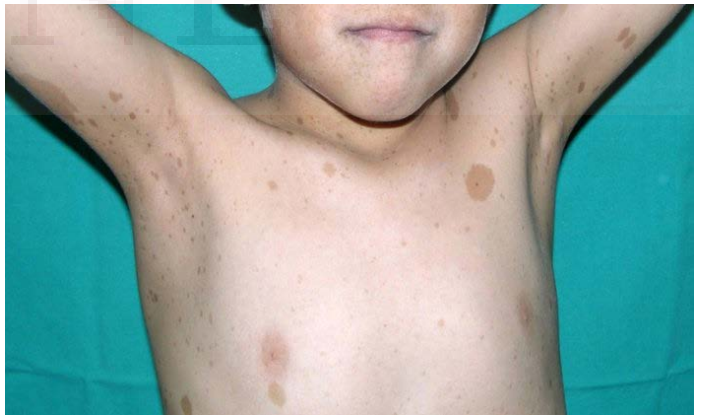
2c – pheocrhomocytoma, no hemangioblastomas, no renal cell carcinomas.

Patients have mutations in VHL gene.

- **NF type 1 (Von Recklinghausen):**
  - autosomal dominant pattern
  - optic gliomas, subcutaneous neurofibromas and schwannomas of cranial and vertebral nerve roots, freckles in their axillae and skin folds, café au lait spots.

Mutations in NF1 gene.





Succinate dehydrogenase gene mutations:

- **SDHB**: paragangliomas (frequently sympathetic all along sympathetic chains from head to pelvis), pheochromocytomas.

- **SDHD**: paragangliomas (frequently parasympathetic paragagliomas of head and neck that do not secrete catecholamines), pheochromocytomas.

Who should be screened?

Clinical Cancer Research

Clinical Predictors and Algorithm for the Genetic Diagnosis of Pheochromocytoma Patients

Zoran Erlic, Lisa Rybicki, Mariola Peczkowska, et al.

Clin Cancer Res 2009;15:6378-6385. Published OnlineFirst October 14, 2009.

Table 1. Demographic and clinical data of the patients included in the analysis

Variable	All patients			Mutation positive patients							
	N_{total}	Any mutation	%	SDHB	%	VHL	%	RET	%	SDHD	%
Sex											
Male	425	97	22.8	39	40.2	32	33.0	12	12.4	14	14.4
Female	564	90	16.0	34	37.8	23	25.6	19	21.1	14	15.6
Age											
≤45	521	158	30.3	56	35.4	52	32.9	23	14.6	27	17.1
>45	468	29	6.2	17	58.6	3	10.3	8	27.6	1	3.4
Tumor biology											
Benign	901	162	18.0	53	32.7	51	31.5	31	19.1	27	16.7
Malignant	88	25	28.4	20	80.0	4	16.0	0	0	1	4.0
Tumor number											
Single	818	94	11.5	52	55.3	22	23.4	9	9.6	11	11.7
Multiple	171	93	54.4	21	22.6	33	35.5	22	23.7	17	18.3
Tumor location											
Adrenal mono-/bilateral	816	111	13.6	24	21.6	45	40.5	31	27.9	11	9.9
Extra-adrenal abd/pelvic/thoracic	135	56	41.5	45	80.4	4	7.1	0	0	7	12.5
Extra-adrenal and adrenal	38	20	52.6	4	20.0	6	30.0	0	0	10	50.0
Previous HNP											
Yes	25	22	88.0	6	27.3	0	0	0	0	16	72.7
No	964	165	17.1	67	40.6	55	33.3	31	18.8	12	7.3
Family history											
Positive	42	17	40.5	14	82.4	0	0	0	0	3	17.6
Negative	947	170	18.0	59	34.7	55	32.4	31	18.2	25	14.7
Total	989	187	18.9	73	39.0	55	29.4	31	16.6	28	15.0

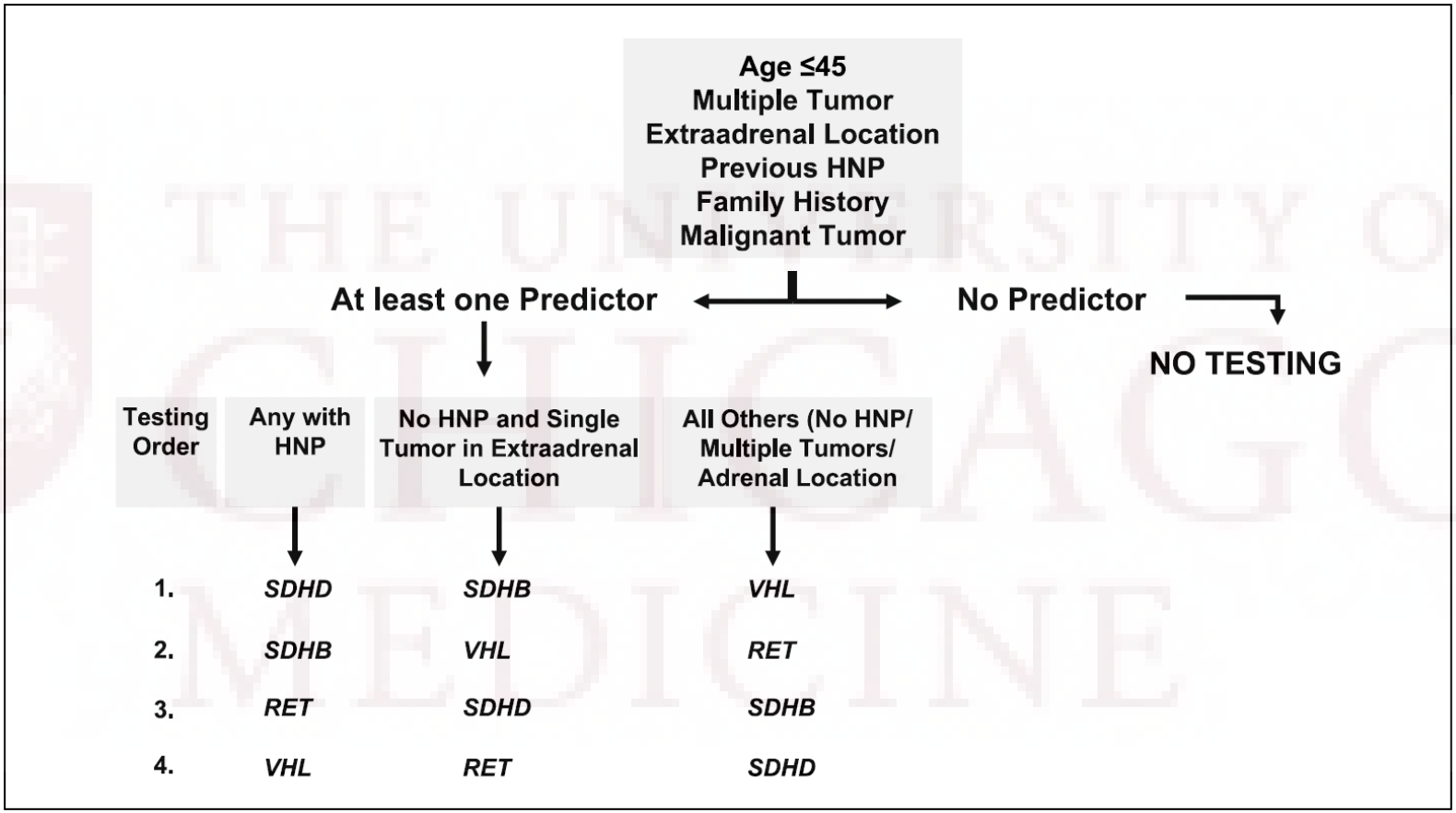
Erlic Z, Rybicki L, Peczkowska M, Golcher H, Kann PH, Brauckhoff M, Müssig K, Muresan M, Schäffler A, Reisch N, Schott M, Fassnacht M, Opocher G, Klose S, Fottner C, Forrer F, Plöckinger U, Petersenn S, Zabolotny D, Kollukch O, Yaremchuk S, Januszewicz A, Walz MK, Eng C, Neumann HP; European-American Pheochromocytoma Study Group. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. Clin Cancer Res. 2009 Oct 15;15(20):6378-85

Table 2. Univariable and multivariable logistic regression analysis results for presence of any germline mutation

Variable	Univariable		Multivariable*		Bootstrap assessment of risk factors†
	OR (95% CI)	*P*	OR (95% CI)	*P*	
Gender					
Male/female	1.56 (1.13-2.14)	0.007	1.32 (0.90-1.95)	0.16	26.1%
Age (y)					
<45/>45	6.59 (4.33-10.02)	<0.001	5.37 (3.34-8.62)	<0.001	99.8%
Tumor biology					
Malignant/benign	1.81 (1.10-2.96)	0.018	1.35 (0.71-2.59)	0.36	15.2%
Tumor number					
Multiple/single	9.18 (6.34-13.29)	<0.001	8.78 (5.47-14.08)	<0.001	100.0%
Tumor location					
Extra-adrenal/adrenal	4.50 (3.03-6.69)	<0.001	4.93 (3.00-8.10)	<0.001	99.5%
Ad&ex/adrenal	7.06 (3.62-13.76)	<0.001	0.76 (0.34-1.70)	0.50	
Other tumors (HNP)					
Yes/No	35.51 (10.51-120.0)	<0.001	11.95 (3.15-45.32)	<0.001	92.4%
Family history					
Positive/negative	3.11 (1.64-5.88)	<0.001	2.07 (0.94-4.55)	0.07	40.9%

Erlic Z, Rybicki L, Peczkowska M, Golcher H, Kann PH, Brauckhoff M, Müssig K, Muresan M, Schäffler A, Reisch N, Schott M, Fassnacht M, Opocher G, Klose S, Fottner C, Forrer F, Plöckinger U, Petersenn S, Zabolotny D, Kollukch O, Yaremchuk S, Januszewicz A, Walz MK, Eng C, Neumann HP; European-American Pheochromocytoma Study Group. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. Clin Cancer Res. 2009 Oct 15;15(20):6378-85

Genetic testing algorithm:

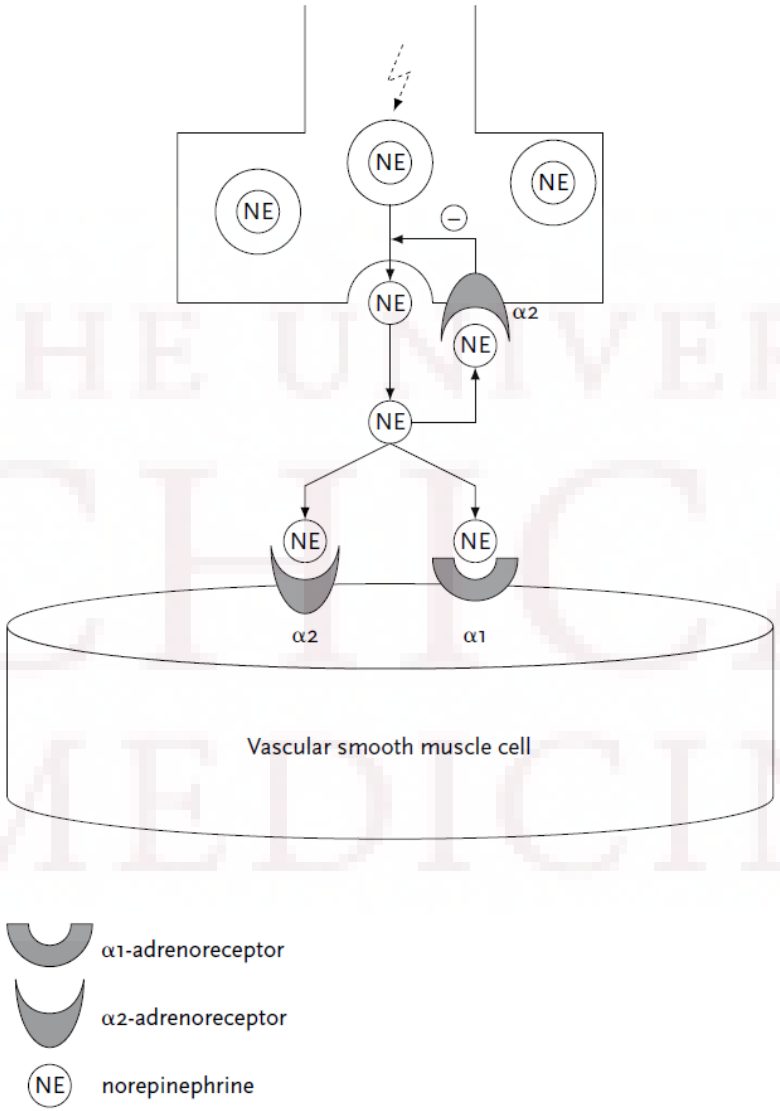


Erlic Z, Rybicki L, Peczkowska M, Golcher H, Kann PH, Brauckhoff M, Müssig K, Muresan M, Schäffler A, Reisch N, Schott M, Fassnacht M, Opocher G, Klose S, Fottner C, Forrer F, Plöckinger U, Petersenn S, Zabolotny D, Kollukch O, Yaremchuk S, Januszewicz A, Walz MK, Eng C, Neumann HP; European-American Pheochromocytoma Study Group. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. Clin Cancer Res. 2009 Oct 15;15(20):6378-85

Preoperative management of pheochromocytoma:

- Goal to lower BP to 130/85 or less while avoiding symptomatic orthostasis
- α-blockade for 1-2 weeks prior to surgery
- Selective and non selective α-blockers
- **Non-selective α-blockers**: phenoxabenzamine at a starting dosage 10mg/day, can be titrated up to 100mg/day.
- Side-effects: reflex tachycardia due to inhibition of α2 receptors, prolonged duration of action - risk for postoperative tachycardia, central sedation.

Figure 1. *Mechanism of action of α_1- and α_2-adrenoreceptor antagonists*



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Preoperative management of pheochromocytoma:

- **Selective α-blockers:** doxazosin (2-16mg/day) and prazosin (2-20mg/day).
- Benefits: no reflex tachycardia, shorter duration of action.
- Do selective α-blockers are superior to nonselective α-blockers?

Efficacy and Safety of Doxazosin for Perioperative Management of Patients with Pheochromocytoma

Cedric Prys-Roberts, D.M., Ph.D.,[1] John R. Farndon, B.Sc., M.D.[2]

[1]Sir Humphry Davy Department of Anaesthesia, University of Bristol, Level 7, Bristol Royal Infirmary, Bristol, BS2 8HW, UK
[2]Department of Surgery, University of Bristol, Bristol Royal Infirmary, Bristol, BS2 8HW, UK

Table 1. Patients and their diagnoses, pretreatment urinary catecholamine concentrations, preoperative drug therapy, and survival.

Parameter	Phenoxybenzamine	Doxazosin
Patient characteristics		
Males	3	8
Females	5	19
Age (years), median and range	45.5 (19–67)	46.7 (17–79)
Weight (kg), median and range	61.5 (45–68)	71.3 (34–110)
Pheochromocytoma		
Right adrenal	3	13
Left adrenal	4	10
Bilateral	—	2
Other tumor (paraganglionoma)	1	2
Phenoxybenzamine, daily dose (mg)	20–150	—
Doxazosin, daily dose (mg)		
2	—	6
4	—	10
6–8	—	10
16	—	1
Survival (no. alive and well/total)	6/8	26/27
Urinary assays		
Norepinephrine (nmol/24 hr)		
< 800 (uln)	—	5
800–5000	—	5
> 5000	1	16
Epinephrine (nmol/24 hr)		
< 100 (uln)	—	12
100–500	—	7
> 500	1	8
Dopamine (nmol/24h)		
< 3000 (uln)	—	14
> 3000	1	5

uln: upper limit of normal values.

Table 2. Blood pressures and heart rate measured preoperatively, during stable anesthesia before tumor handling, during tumor handling, and during the first hour postoperatively.[a]

Time of measurements	Phenoxybenzamine (n = 8)	Doxazosin (n = 27)	p	Doxazosin (laparoscopic) (n = 9)
Preoperative values				
SAP (mmHg)	162 (17.7)	148 (21.1)	0.195	
DAP (mmHg)	92 (15.3)	78 (13.6)	0.029	
HR (beats/min)	71 (12.6)	72 (11.5)	0.451	
During stable anesthesia				
SAP (mmHg)	98 (5.9)	97 (6.9)	0.705	
DAP (mmHg)	59 (7.6)	52 (6.5)	0.049	
HR (beats/min)	51 (3.7)	59 (5.0)	0.003	
Peak values during tumor handling (n = 18)				
SAP (mmHg)	185 (32.5)	178 (29.9)	0.659	199 (29.9)
DAP (mmHg)	102 (14.4)	95 (17.3)	0.373	103 (12.0)
HR (beats/min)	94 (9.7)	78 (13.9)	0.013	83 (9.8)
Peak postoperative values (1st hour after surgery) (n = 18)				
SAP (mmHg)	100 (11.9)	116 (14.8)	0.004	122 (14.8)
DAP (mmHg)	55 (7.1)	64 (8.5)	0.007	61 (6.5)
HR (beats/min)	61 (6.9)	71 (10.1)	0.010	70 (8.9)
Drug administration[a]				
Phentolamine (mg)	9.6 (6.8)	11.1 (7.6)	0.652	12.9 (range 1–34)
Labetalol (mg)	33.1 (8.4)	15.8 (8.2)	0.080	32.5 (n = 4)

Prys-Roberts C. et al. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. World J Surg. 2002 Aug;26(8):1037-42. Epub 2002 Jun 19.

- Another retrospective study was not able to demonstrate a difference between phenoxybenzamine, doxazosin and prazosin with respect to BP control and amount of postoperative fluid replacement.[1]

- Another report with only four patients, adequate BP control was not achieved with prazosin, which even resulted in postponement of surgery in one patient.[2]

[1]Kocak S, Aydintug S, Canakci N. Alpha blockade in preoperative preparation of patients with phaeochromocytomas. Int Surg 2002;87:191-4.

[2]Nicholson JP Jr, Vaughn ED Jr, Pickering TG, et al. Phaeochromocytoma and prazosin. Ann Intern Med 1983;99:477-9.

Pheochomocytoma and rhabdomyolysis:

Case number, year of publication	References	Age & sex
1 (1984)	Oristrell-Salva et al.	47 M
2 (1986)	Bhatnagar et al.	54 M
3 (1990)	Shemin et al.	29 F
4 (2003)	Schumann et al.	34 M
5 (2005)	Onozava et al.	47 F
6 (2008)	Anaforoglu et al.	19 M
7 (2011)	Takahashi et al.	66 F
8 (2012)	Ende et al.	45 F

Pheochomocytoma and rhabdomyolysis:

- Proposed mechanism is cathacholamine induced vasoconstriction leading to skeletal muscle injury, disruption of muscle cell integrity, and release of the intracellular contents of the muscle cells into the extracellular space.

Summary:

- Pheochromocytoma is a rare tumor that can occur sporadically or as part of a syndrome
- Patients younger than 45, patients with malignant pheochromocytoma, bilateral pheochromocytoma and patients with other tumors need to be genetically tested
- Rhabdomyolysis can happen in pheochromocytoma secondary to vasoconstriction leading to skeletal muscle cell injury
- Patient should be treated with α-blockers for 1-2 weeks prior to surgery

References:

- Erlic et al. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. Clin Cancer Res. 2009 Oct 15;15(20):6378-85
- Pacak K *et al.* (2007) Pheochromocytoma: recommendations for clinical practice from the First International Symposium *Nat Clin* Pract Endocrinol Metab 3: 92-102
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- Prys-Roberts C. et al. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. World J Surg. 2002 Aug;26(8):1037-42. Epub 2002 Jun 19
- Kocak et al. Alpha blockade in preoperative preparation of patients with phaeochromocytomas. Int Surg 2002;87:191-4
- Nicholson JP Jr et al. Phaeochromocytoma and prazosin. Ann Intern Med 1983;99:477-9